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Three-dimensionally printed surface features to anchor endoluminal spring for distraction enterogenesis.

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Journal

PloS one, 13(7)

ISSN

1932-6203

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Publication Date

2018

DOI

10.1371/journal.pone.0200529

Peer reviewed

RESEARCH ARTICLE

Three-dimensionally printed surface features to anchor endoluminal spring for distraction enterogenesis

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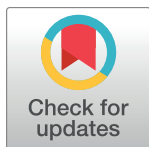
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OPEN ACCESS

Citation: Huynh N, Dubrovsky G, Rouch JD, Scott A, Chiang E, Nguyen T, et al. (2018) Three-dimensionally printed surface features to anchor endoluminal spring for distraction enterogenesis. PLoS ONE 13(7): e0200529. <https://doi.org/10.1371/journal.pone.0200529>

Editor: Christina Chan, Michigan State University, UNITED STATES

Received: June 25, 2017

Accepted: June 28, 2018

Published: July 12, 2018

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This study was funded by Sun West Company and the Coulter Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: This study was partly funded by Sun West Company. There are no patents, products in development or marketed products to

Abstract

Spring-mediated distraction enterogenesis has been studied as a novel treatment for short bowel syndrome (SBS). Previous approaches are limited by multiple surgeries to restore intestinal continuity. Purely endoluminal devices require a period of intestinal attachment for enterogenesis. The purpose of this study is to modify the device to prevent premature spring migration in a porcine model. Two models were created in juvenile mini-Yucatan pigs for the placement of three-dimensionally printed springs. (1) Two Roux-en-y jejunojejunostomies with two Roux limbs were made. A spring with bidirectional hooked surface features was placed in one Roux limb and a spring with smooth surface was placed in the other Roux limb. (2) The in-continuity model had both hooked and smooth surface springs placed directly in intestinal continuity. Spring location was evaluated by weekly radiographs, and the intestine was retrieved after 2 to 4 weeks. Springs with smooth surfaces migrated between 1 to 3 weeks after placement in both porcine models. Springs with bidirectional hooked surface features were anchored to the intestine for up to 4 weeks without migration. Histologically, the jejunal architecture showed significantly increased crypt depth and muscularis thickness compared to normal jejunum. Bidirectional features printed on springs prevented the premature migration of endoluminal springs. These novel spring anchors allowed for their endoluminal placement without any sutures. This approach may lead to the endoscopic placement of the device for patients with SBS.

declare. This does not alter our adherence to all the PLOS ONE policies on sharing data and materials, as detailed online in the guide for authors.

Introduction

Short bowel syndrome (SBS) is a disease of the small intestine caused by inadequate intestinal length, which leads to poor nutritional absorption and total parental nutrition dependence complicated by infections and liver failure [1]. Healthcare costs associated with this condition exceed \$3 billion USD annually [2–3]. SBS is a result of extensive intestinal resection from necrotizing enterocolitis, intestinal atresia, and midgut volvulus [4]. Current surgical procedures to increase intestinal surface area and slow intestinal transit have had limited success [4–7]. New therapeutic modalities are needed.

Distraction enterogenesis to lengthen existing intestines has been studied to address the underlying issue of SBS. Multiple devices including hydraulic pistons, saline injections, and anchored screws have been successful in the application of distractive forces to lengthen intestines in animal models [8–14]. Our laboratory demonstrated effective intestinal lengthening using spring-mediated distractive devices [15–21]. However, these models are limited by multiple surgeries to repeat intestinal lengthening, restore intestinal continuity, or require extraluminal attachments [15,18,20,22–23].

Minimally invasive or endoscopically placed spring devices can avoid such limitations and facilitate clinical application for SBS. Purely endoluminal devices require a period of intestinal attachment for enterogenesis [15]. Spring designs must overcome the digestive tract's intrinsic properties to contract and expel foreign material into the feces. Similar issues of esophageal and colonic stent migration are noted in other areas of the digestive tract [24–26]. Previously, we developed a high-friction surface spring that evenly distributes distractive forces along the intestinal wall to delay spring detachment, but premature spring migration remained a challenge [15].

Three-dimensional (3D) printing has been widely utilized to create medical models and devices [27–29]. Resolution of 3D-printers is as small as 16 microns [30]. Sophisticated 3D-printing technology can print surface features directly on the springs and optimize surface structures to enhance spring attachment. The purpose of this study is to modify the surface of springs to adequately anchor springs to intestines in a porcine model.

Materials and methods

Ethics statement

The use of animals was approved by the University of California, Los Angeles Animal Research Committee (Institutional Review Board Number 2014-142-03 and 2016-002-02A). Vaporized isoflurane was used for anesthesia and phenobarbital was used for euthanasia. All materials were FDA approved for use in humans.

Spring production and characteristics

Spring models were designed on Fusion Autodesk 360 (Autodesk, San Rafael, CA). Spring model files were sent for 3D-printing to a commercialized manufacturer (Sculpteo, Villejuif, France). A selective laser sintering (SLS) process was used to print the springs [31]. The 3D-printed spring was made from nylon, a biocompatible polymer used in sutures [32].

Spring characteristics were extrapolated from previous study of spring with high-friction villi-like surface features in pigs [15]. 3D-printed spring surface features were designed with bidirectional angulated structures to hook onto the intestinal wall (Fig 1). Spring dimensions measured 13 to 14 mm in outer diameter, compressed length of 25 mm, and expanded length of 50 to 70 mm. Smooth surface springs were used for comparison. The springs were placed

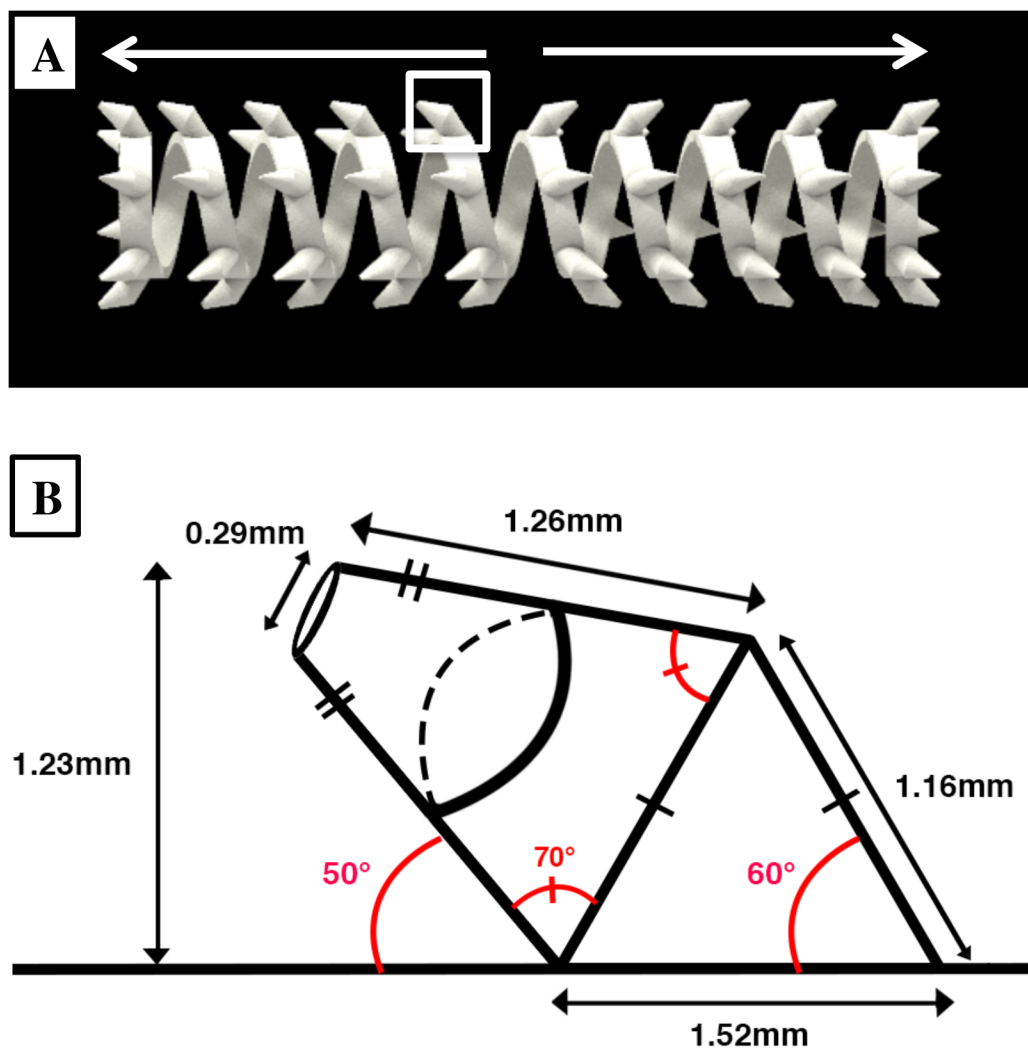


Fig 1. Image of three-dimensionally printed spring with angled bidirectional surface features. (A) Direction of features is indicated by the arrows. One of the surface hooks is isolated by a box. Scale bar is 5 mm. (B) Zoomed in side view schematic of isolated surface feature and corresponding dimensions.

<https://doi.org/10.1371/journal.pone.0200529.g001>

into size 13 Gelatin capsules (Torpac, Inc, Fairfield, NJ) and were coated three times with cellulose acetate phthalate for delayed expansion (Eastman Chemicals, Kingsport, TN) [33].

Surgical procedure

Female juvenile mini-Yucatan pigs *Sus scrofa* (S & S Farms), 4 to 6 weeks old, weighing at least 5 kg were intubated, anesthetized with inhaled oxygen, and vaporized isoflurane (n = 9). A midline laparotomy incision was used to enter the abdomen. Two animal models were created.

Roux-en-y jejunojejunostomies. Two Roux-en-y jejunojejunostomies with two 30-cm defunctionalized blind end Roux limbs were created in the proximal jejunum. The jejunum was transected 30 cm from the ligament of Trietz to create the first Roux limb. The second Roux limb was created 30 cm from the first jejunojejunostomy (n = 4) (Figs 2 and 3). In two animals, one Roux limb was made into a stoma for sequential spring placement (Fig 2). An

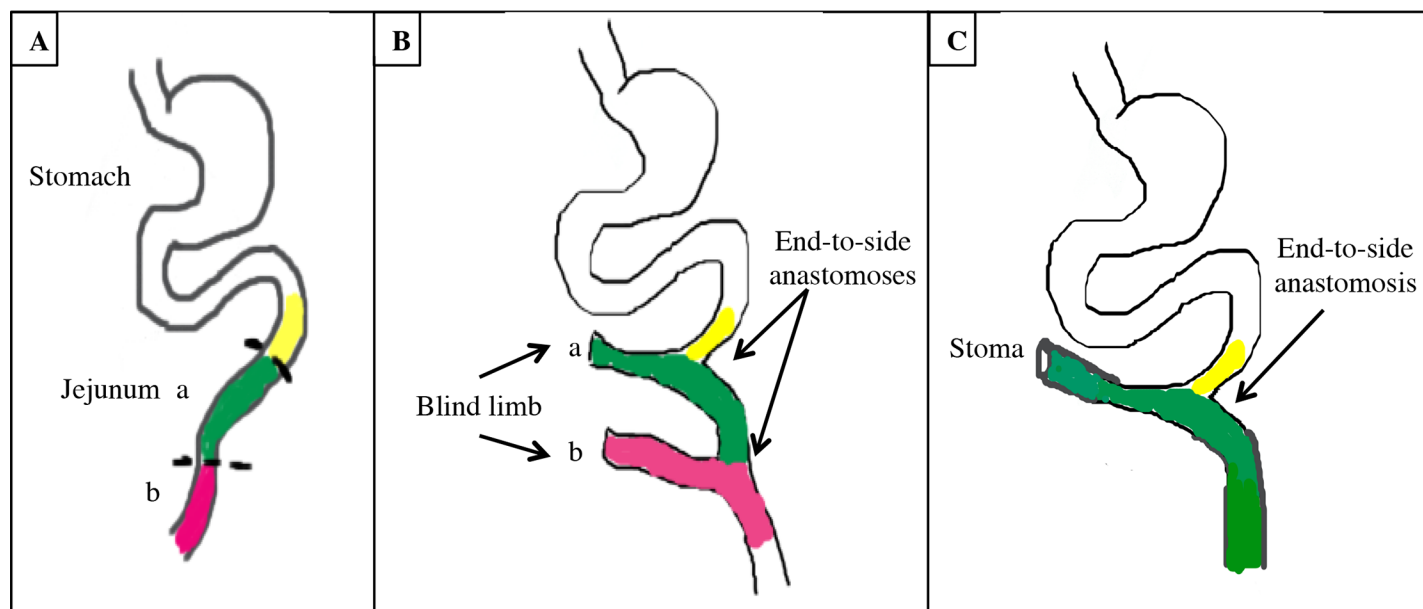


Fig 2. Schematic of Roux-en-y model. (A) Jejunum prior to surgery: *a* is proximal jejunum, *b* is distal jejunum; (B) Roux-en-y jejunojejunostomies with two blind jejunal limbs and end-to-side anastomoses; (C) stoma model with Roux limb and end-to-side anastomosis.

<https://doi.org/10.1371/journal.pone.0200529.g002>

encapsulated 3D-printed spring with surface features was inserted in one limb and an encapsulated smooth surface spring was inserted in the other limb (Fig 3). The Roux limb ends were closed with 4–0 Prolene suture (Ethicon, Johnson & Johnson; Somerville, NJ) in simple interrupted fashion. The jejunojejunostomies were repaired with end-to-side anastomoses with 4–0 Prolene in simple interrupted fashion to restore intestinal continuity.

In-continuity spring placement. A subset of animals ($n = 3$) underwent in-continuity spring placement. The jejunum was transected 30 cm from the ligament of Trietz. An encapsulated 3D-printed spring with hooked surface features was placed proximal to the transected

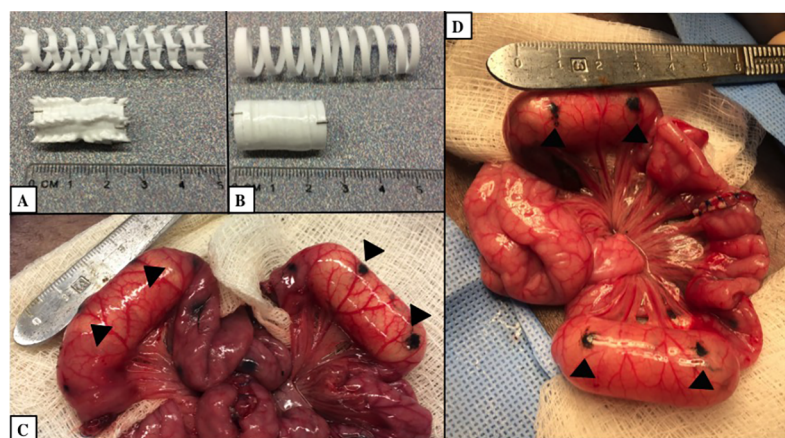


Fig 3. Image of springs in Roux-en-y and in-continuity models. (A) Representative photos of expanded and compressed springs with hooked surface features and (B) smooth surface. (C) Operative image showing Roux-en-y configuration with two blind Roux limbs with the hooked spring placed in the Roux limb on the left of the image and smooth spring placed in the Roux limb on the right of the image. (D) Operative image showing in-continuity model with hooked spring proximal to anastomosis and smooth spring distal to anastomosis. Arrowheads mark areas of India ink injected at the ends of the compressed springs.

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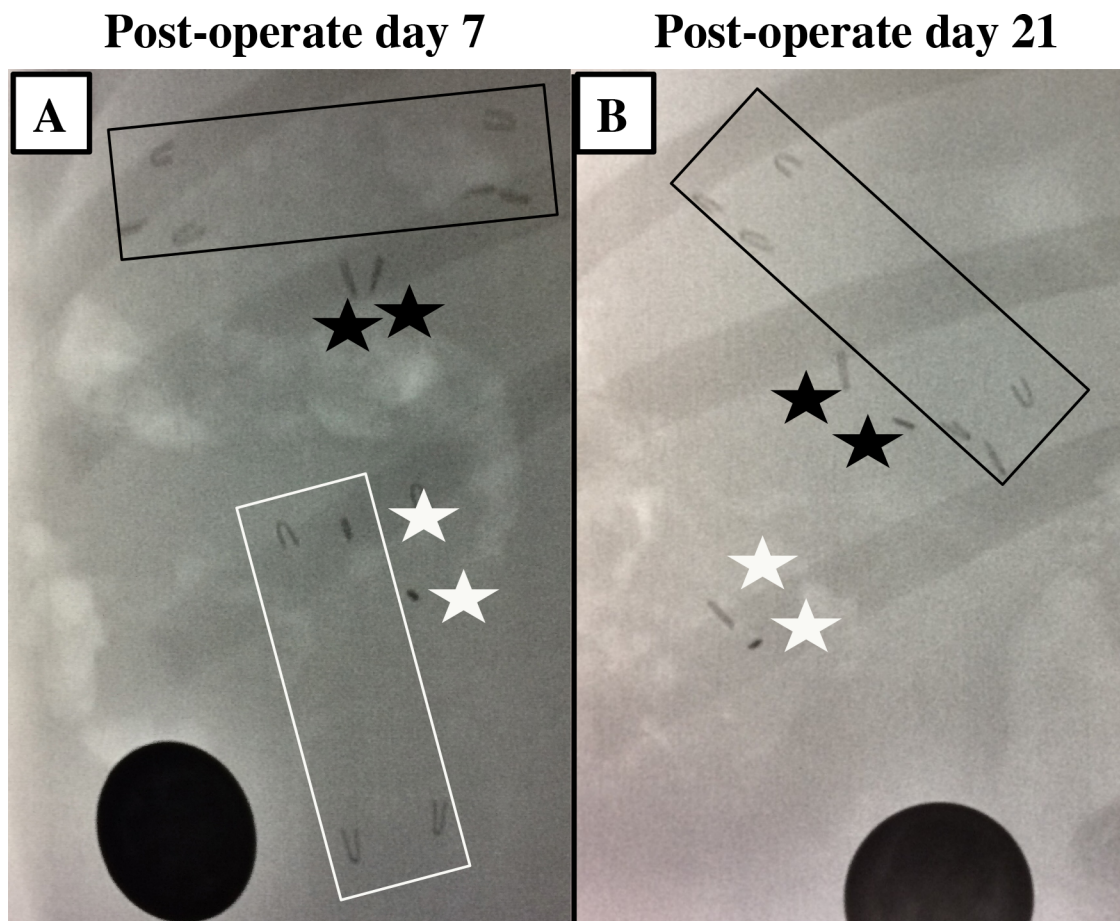


Fig 4. Abdominal radiographs of spring placement. Radiographs show metal clips at the ends of the spring and on adjacent mesentery on (A) post-operative day 7 and (B) post-operative day 21. Hooked spring is labeled with three metal clips at each end, shown in black box. Smooth surface spring is labeled with two metal clips at each end, shown in white box. The smooth surface spring had migrated by post-operative day 21. Stars mark the mesenteric clips. Scale object measurement is 2.1 cm in diameter.

<https://doi.org/10.1371/journal.pone.0200529.g004>

jejunum. An encapsulated 3D-printed smooth surface spring was inserted distal to the transected jejunum (Fig 3). The transected jejunum was repaired with an end-to-end anastomosis with 4-0 Prolene suture in a simple interrupted fashion to restore intestinal continuity.

In both animal models, metal clips were placed on each end of the spring and on the mesentery adjacent to the spring ends in order to monitor spring expansion on weekly abdominal x-rays (Fig 4). India ink (Becton, Dickinson and Company, Franklin Lakes, NJ) was injected at the ends of the compressed spring to evaluate initial location of springs upon specimen retrieval. The bowel was placed back into the abdomen and the abdominal wall was closed in layers.

Animals with in-continuity springs were placed on a fortified liquid diet. Animal weights were recorded. Animals were euthanized with phenobarbital and intestinal segments were retrieved after 2, 3, and 4 weeks for final assessment of spring location.

Histologic analysis

Jejunum marked with India ink and normal jejunum were fixed in 10% buffered formalin overnight followed by embedding in paraffin. Normal jejunum used for comparison was

jejunum in the Roux limb without the hooked spring in the Roux-en-y model and jejunum without the hooked spring in the in-continuity model. Tissue was aligned in perpendicular cross sections. Tissue blocks were cut into 5 μm sections and stained with hematoxylin and eosin. Sections were examined and recorded at 4x and 10x magnification using light microscopy (Olympus Corporation, Waltham, MA). Muscularis propria thickness and crypt depth were measured for each specimen.

Statistical analysis

Data were expressed as mean values \pm standard deviations. Two-tailed, paired and unpaired Student's t-tests were used for statistical analyses where appropriate.

Results

Animals tolerated the procedure well without signs of obstruction or perforation. Roux-en-y animals demonstrated weight gain of 137 ± 42 grams per day. In-continuity animals gained 83 ± 20 grams per day.

Duration of spring attachment

All springs with smooth surfaces migrated from the initial location into the fecal stream between 1 to 3 weeks after placement. Springs with bidirectional surface features were anchored to the intestine for the entire duration without migration as evaluated by weekly abdominal radiographs. These findings were confirmed at time of specimen retrieval at 2, 3 and 4 weeks after placement (Fig 5).

Histological analysis

Histologically, jejunal architecture was preserved in intestinal segments with hooked 3D-printed springs. Roux limb jejunum with hooked springs showed significantly increased crypt depth ($438 \pm 106 \mu\text{m}$ versus $204 \pm 43 \mu\text{m}$; $p = 0.001$) and muscularis thickness ($782 \pm 332 \mu\text{m}$ versus $230 \pm 128 \mu\text{m}$; $p = 0.01$) in comparison to Roux limb jejunum without hooked springs. In-

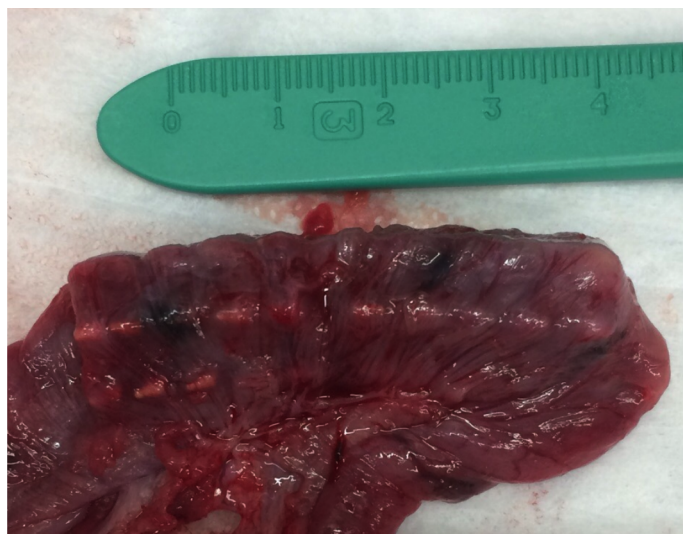


Fig 5. Intestinal segment at time of specimen retrieval. Intestinal segment with fully expanded hooked spring at time of specimen retrieval on post-operative day 28.

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continuity jejunum with hooked springs showed a greater degree of increased crypt depth in comparison to jejunum without hooked springs ($656 \pm 46 \mu\text{m}$ versus $353 \pm 86 \mu\text{m}$; $p = 0.006$). Muscularis thickness of these segments was similarly thickened ($733 \pm 164 \mu\text{m}$ versus $362 \pm 60 \mu\text{m}$; $p = 0.02$) (Fig 6).

Discussion

Previous anchoring techniques employed a high-friction surface on the spring to evenly distribute distractive forces along the intestinal length to delay spring detachment [15]. In this study, spring surface features were modified to further delay premature spring migration. This novel spring with enhanced spring-to-bowel coupling is suitable for endoscopic delivery and negates the need for complex anchoring techniques or additional surgeries for sequential spring placement.

Spring-mediated distraction enterogenesis successfully demonstrated intestinal lengthening in animal models with a few barriers to clinical application. The animal models and spring characteristics have evolved to address these limitations. Prior to this study, an isolated jejunal segment model was utilized to study spring-mediated intestinal lengthening [17–18]. Although lengthening was 3-fold in rodents, the clinical impact was limited by tissue loss during restoration into continuity and multiple surgeries [18]. Roux-en-y jejunojejunostomy was then used as a model for repeated spring placements but required extraluminal attachments to anchor springs [20]. The in-continuity model was developed to avoid extensive bowel manipulation and multiple surgeries [15]. Although this model was safe and feasible, premature spring migration prevented adequate time for maximal distraction enterogenesis [15]. Addition of a high-friction surface delayed spring migration however full-thickness sutures were still required to anchor the spring [15]. This current study successfully demonstrated that angulated, bidirectional surface features enhanced spring attachment and prevented spring migration.

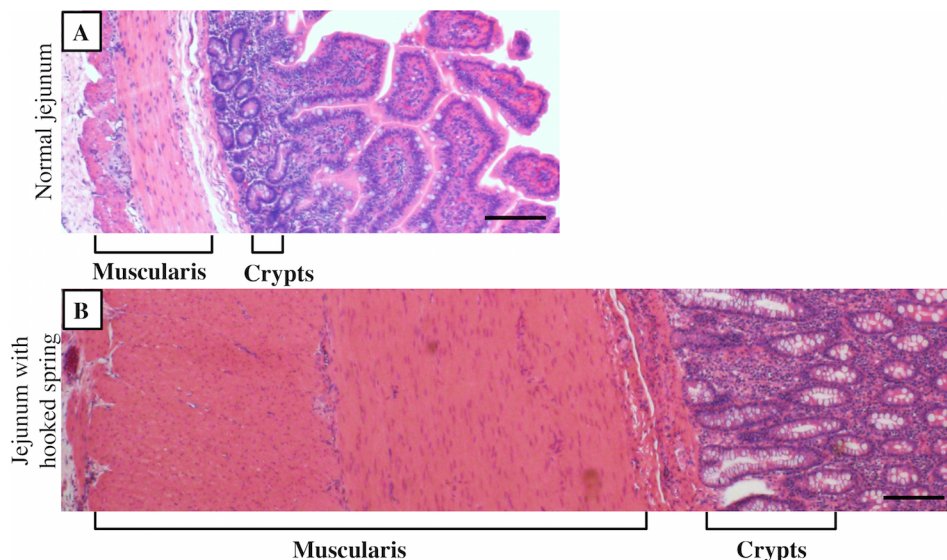


Fig 6. Histology of jejunum with spring versus normal jejunum. Jejunal segments with hooked spring demonstrate significantly increased crypt depth and muscularis propria thickness relative to normal jejunum without spring. Light microscopy images of hematoxylin and eosin-stained (A) normal jejunum without spring and (B) jejunum with hooked spring in-continuity at 4× magnification. Scale bar is 100 μm .

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Bidirectional surface features were designed to accommodate the dynamic back and forth motion of peristalsis. Hooks in each direction assist in anchoring the spring in place. The hooked springs are delivered intraluminally inside a smooth gelatin capsule to avoid damage to intestinal epithelium. Once the capsule dissolves, the hooks on the spring engage to the intestinal wall.

The Roux-en-y jejunojejunostomy model was used to study the effectiveness in anchoring the hooked spring. The two limbs allowed for an internal control spring to be studied simultaneously with the hooked spring. We recognize that other surgical models are more telling of potential clinical application [15,22]. Once the hooked features demonstrated adequate anchoring, the novel spring was placed via a defunctionalized stoma and allowed for sequential manual spring insertion via stoma without additional surgeries needed for spring placement. The spring did not migrate. To avoid excessive bowel manipulation and evaluate the potential for endoscopic spring placement, springs were inserted in direct enteric continuity and demonstrated no spring migration. Further studies in these prototypical animal models is needed to conclude effectiveness but these preliminary studies is proof-of-concept that the novel hooked spring can be delivered in a minimally invasive fashion, endoscopically, or manually via stoma in a repeatable fashion.

Although these nylon springs are biocompatible, it is not biodegradable. Previous studies used polycaprolactone (PCL) to create biodegradable springs to avoid a procedure to retrieve the spring at a later time [18]. 3D-printers with PCL printing capabilities do not have sufficient resolution to produce the small surface features at this time, and non-degradable materials were used for this study as a proof-of-concept. Previous studies have shown that springs eventually detached and spontaneously passed in the fecal stream without causing complications; thus a biodegradable material may not be necessary. The hooked spring has spring constant of 45 N/m, which is three times that of the PCL spring used in our previous studies. The larger spring constant may lead to faster expansion of the spring once the gelatin capsule dissolves before the necessary engagement of the spring to the bowel could take place. Nevertheless, the hooks allowed the spring to remain in place albeit in an expanded state. The spring constant is determined by the material and physical aspects of the spring including the width of the band of the spring. Currently the width is larger than previous PCL springs to accommodate the base of the hooks. Additional spring designs are under investigation to adjust the spring constant.

The current spring does not show significant intestinal lengthening. While desirable, intestinal lengthening is not the focus of this study. Optimizing spring characteristics to enhance distraction enterogenesis is under ongoing investigation.

Normal jejunum was used as the comparison to analyze histological changes. Therefore, histological changes can be attributed to the effect of the spring on the intestines. Histology of retrieved jejunum demonstrates increased muscularis thickness and crypt depth, which are characteristic features of tissue subjected to distractive force [11,13]. Increased muscularis thickness and crypt depth are well-documented in the literature in labs who study distraction enterogenesis. Nearly all models evaluating use of distraction enterogenesis have reported these histological changes [8–11, 13, 15–22, 34–35]. Previous studies demonstrated cellular proliferation in lengthened segments in association with these histological changes, intact enzymatic function, absorption capability, and intact barrier function [11, 18]. The role of mechanotransduction pathways has been proposed as the mechanism responsible for distraction enterogenesis. Mechanical force is transmitted via cell membrane integrins that activates the FAK pathway leading to downstream signaling that results in cellular proliferation and decreased apoptosis [36, 37]. Additionally, increase in insulin-like growth factor (IGF-I) expression has been localized to the muscularis propria of lengthened segments and could

account for thickened muscularis [38]. In prior studies, intestinal motility and absorptive function remained intact despite muscularis thickening in these animals [19]. Other studies have also demonstrated return to normal muscularis thickness once the physical force is removed [39].

Crypt depth in in-continuity jejunum is significantly increased in comparison to the crypt depth in defunctionalized Roux limbs. Greater degree of crypt depth increase in in-continuity jejunum is likely from exposure to alimentary nutrition. These observations suggest that the mechanical force imparted by the springs result in cellular proliferation, even in the absence of intestinal lengthening. This approach may yield new therapeutic options via the introduction of mechanical loading in the setting of short bowel syndrome.

Conclusion

In summary, bidirectional hooked spring surface features optimized spring to bowel wall coupling and prevented spring migration. Such novel spring anchors permit purely endoluminal spring placement without any sutures. Repeated endoscopic spring placements or manual insertion via stoma is possible. We believe this approach may lead to the clinical application of the device for patients with short bowel syndrome in the future.

Supporting information

S1 File. Data of springs and histological findings.
(XLSX)

Author Contributions

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Data curation: Nhan Huynh, Genia Dubrovsky, Joshua D. Rouch, Elvin Chiang, Shant Shekherdimian.

Formal analysis: Nhan Huynh, Genia Dubrovsky, Joshua D. Rouch, Thomas M. Krummel, James C. Y. Dunn.

Funding acquisition: James C. Y. Dunn.

Investigation: Nhan Huynh, Genia Dubrovsky, Joshua D. Rouch, Elvin Chiang, Tommy Nguyen, Benjamin M. Wu, Shant Shekherdimian, Thomas M. Krummel, James C. Y. Dunn.

Methodology: Nhan Huynh, Genia Dubrovsky, Joshua D. Rouch, Andrew Scott, Elvin Chiang, Tommy Nguyen, Benjamin M. Wu, Shant Shekherdimian, James C. Y. Dunn.

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Resources: Nhan Huynh, Genia Dubrovsky, Joshua D. Rouch, Benjamin M. Wu, Shant Shekherdimian, James C. Y. Dunn.

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Supervision: Shant Shekherdimian, James C. Y. Dunn.

Validation: Nhan Huynh, Joshua D. Rouch, James C. Y. Dunn.

Visualization: James C. Y. Dunn.

Writing – original draft: Nhan Huynh.

Writing – review & editing: Nhan Huynh, Genia Dubrovsky, Joshua D. Rouch, Andrew Scott, Elvin Chiang, Tommy Nguyen, Benjamin M. Wu, Shant Shekherdimian, Thomas M. Krummel, James C. Y. Dunn.

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